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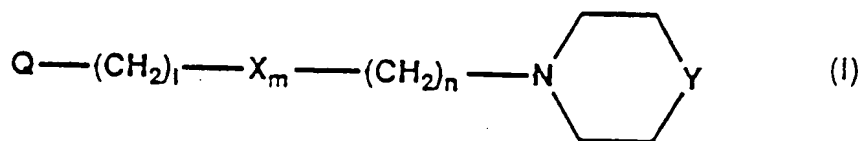
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(54) **Piperidine derivatives and their use as antiarrhythmic agents.**

(57) A piperidine derivative of general formula (I) or a pharmaceutically acceptable salt thereof :



wherein



is any of several specified aromatic-containing groups ; X is selected from one of several hetero atom-containing groups or C₂ alkylene or a cyano-containing group ; and Q is phenyl, cyclohexyl, piperidiny, tetrahydropyranyl, pyridyl, pyrrolyl, N-methylpyrrolyl, thienyl, furyl, 1-hexyl, or cyano ; from 1 to 3 hydrogen atoms in Q may be independently substituted by alkyl of from 1 to 3 carbon atoms, perfluoroalkyl of from 1 to 3 carbon atoms, acylamino of from 1 to 6 carbon atoms, perfluoroacylamino of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, alkanesulfonylamino of from 1 to 3 carbon atoms, perfluoroalkanesulfonylamino of from 1 to 3 carbon atoms, acetoxy of from 1 to 3 carbon

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atoms, aminocarbonyl, aminosulfonyl, fluoro, chloro, cyano, hydroxy, nitro, amino, imidazolylmethyl, cinnamoylamino, p-fluorobenzoyl, cyanomethyl, cyanoethyl, methoxyacetoxy, alkoxycarbonyl of from 1 to 3 carbon atoms ;

1 is an integer of from 0 to 1 ;

m is an integer of from 0 to 1 ;

n is an integer of from 0 to 6.

The derivatives are useful as antiarrhythmic agents.

Field of the Invention

The present invention relates to novel antiarrhythmic agents, more particularly to novel piperidine derivatives and their use in the treatment of arrhythmia.

Background of the Invention

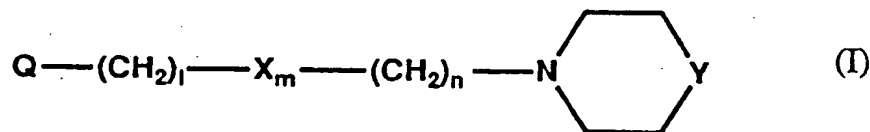
Arrhythmia is the disfunction of cardiac normal conduction, which is a life-threatening disease, because it disturbs the rhythmic beating of the heart, worsening hemodynamics. Therefore, therapy for cardiac arrhythmia is clinically essential.

Antiarrhythmic drugs have been grouped together according to the pattern of mechanism: Na channel blocker, Beta blocker, Ca channel blocker and drugs which prolong Repolarization. Drug therapy of cardiac arrhythmias is not established, because many drugs have severe adverse effects, such as undesirable hemodynamic effects, hypotension, gastrointestinal symptoms, effects on the central nervous system and arrhythmogenic effects. Also, at higher plasma concentrations of drug, cardiac toxicity may become severe, so the monitoring of plasma concentration is essential for drug therapy.

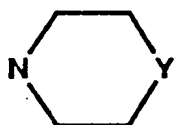
It is therefore required to develop new antiarrhythmic drugs having excellent pharmaceutical effects and safety which can be industrially prepared at low cost in a simple manner.

Disclosure of the Invention

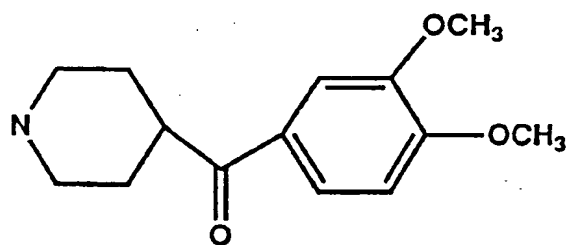
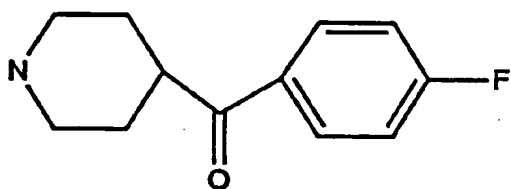
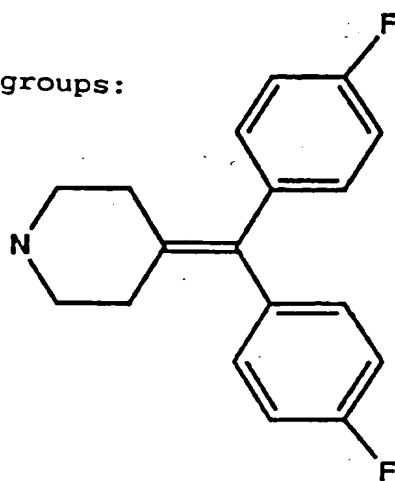
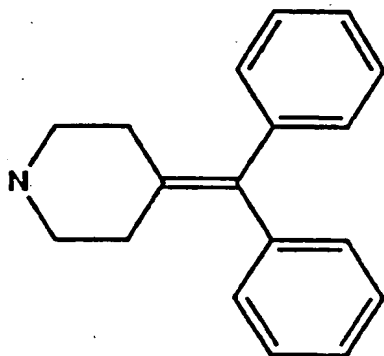
It has now been found that certain piperidine derivatives have antiarrhythmic activity, which derivatives are represented by the following general formula (I):

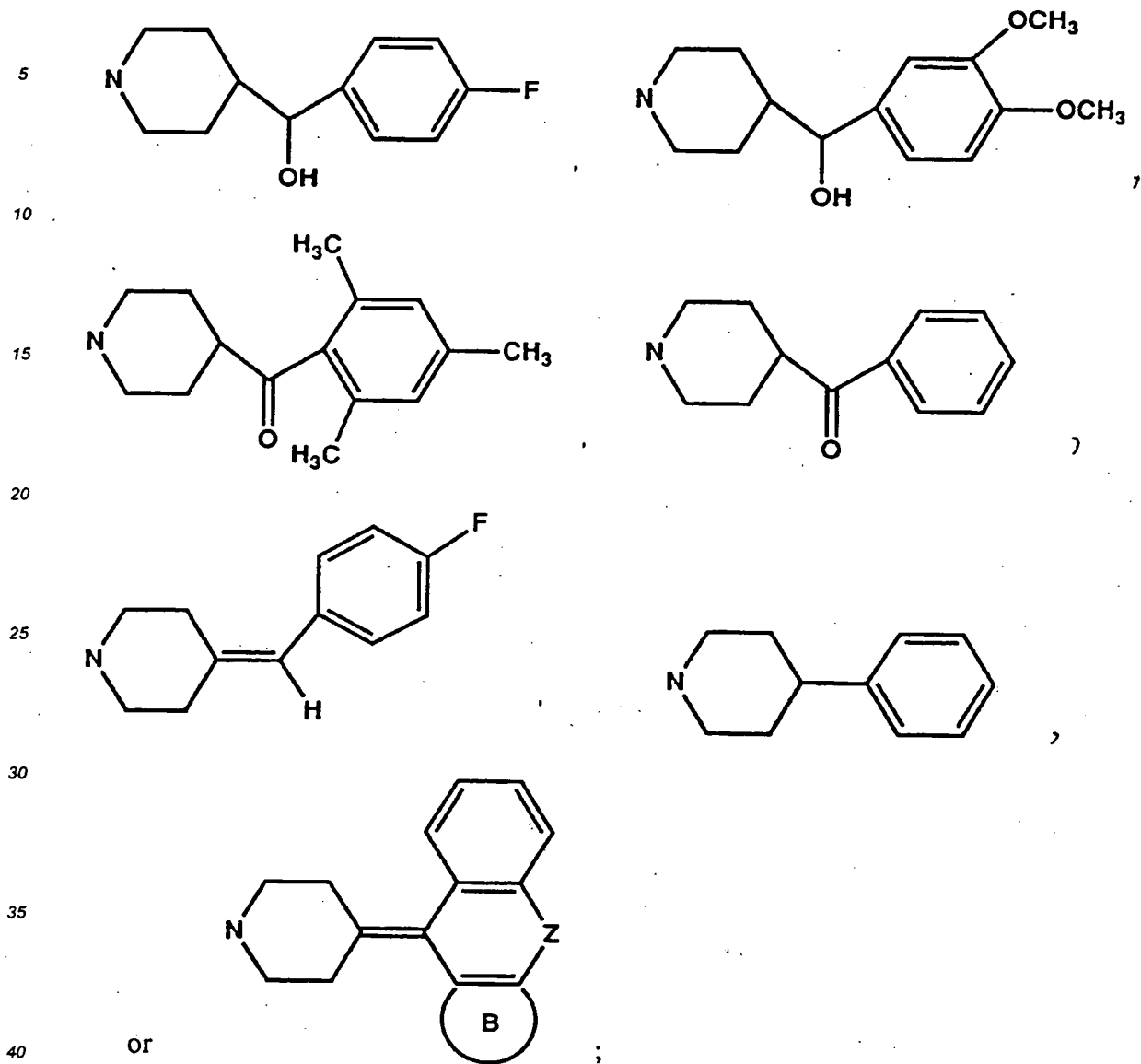


wherein



is any of the following groups:





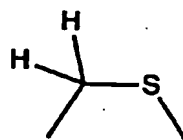
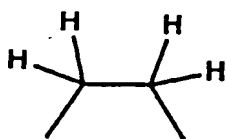
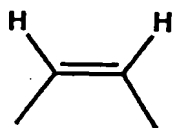
45 wherein B is a fused aromatic or heterocyclic ring selected from the group consisting of benzene, pyridine and thiophene;

50 —Z—

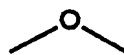
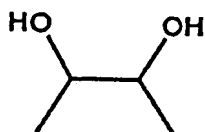
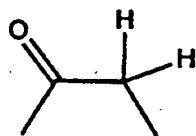
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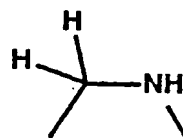
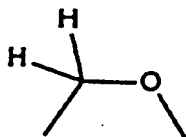
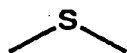


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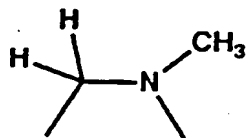
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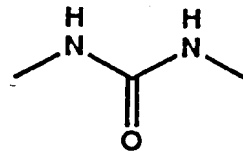
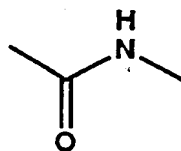
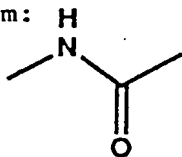
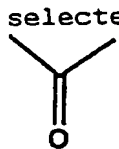
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or

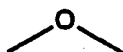
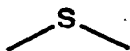
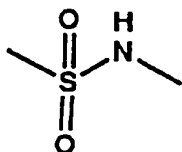


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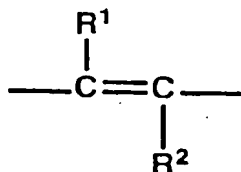


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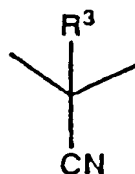


45

50



or



;

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wherein R¹ and R² are the same or different and are independently selected from hydrogen, methyl, ethyl, or propyl; R³ is hydrogen, alkyl of from 1 to 12 carbon atoms, or aryl of from 6 to 12 carbon atoms; Q is phenyl, cyclohexyl, piperidiny, tetrahydropyranyl, pyridyl, pyrrolyl, N-methylpyrrolyl, thienyl, furyl, 1-hexyl, or cyano;

from 1 to 3 hydrogen atoms in Q may be independently substituted by alkyl of from 1 to 3 carbon atoms, perfluoroalkyl of from 1 to 3 carbon atoms, acylamino of from 1 to 6 carbon atoms, perfluoroacylamino of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, alkanesulfonylamino of from 1 to 3 carbon atoms, perfluoroalkanesulfonylamino of from 1 to 3 carbon atoms, acetoxy of from 1 to 3 carbon atoms, aminocarbonyl, aminosulfonyl, fluoro, chloro, cyano, hydroxy, nitro, amino, imidazolymethyl, cinnamoylamino, p-fluorobenzoyl, cyanomethyl, cyanoethyl, methoxyacetoxy, alkoxycarbonyl of from 1 to 3 carbon atoms;

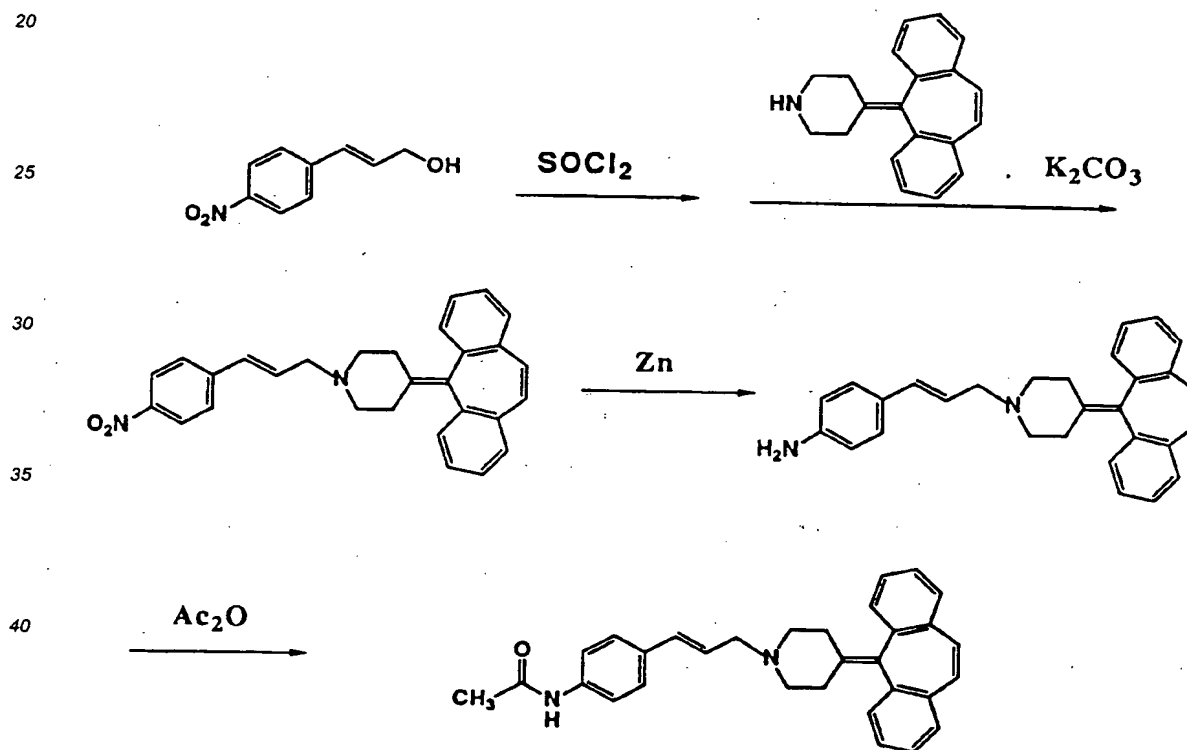
1 is an integer of from 0 to 1;

m is an integer of from 0 to 1;

n is an integer of from 0 to 6.

These compounds may be in their free base form or in the form of a pharmaceutically acceptable salt thereof.

A compound of the above formula can be prepared by the following procedure:



The pharmaceutically acceptable salts of the piperidine derivatives of this invention are acid addition salts formed from the compound and an organic or inorganic acid well known in the art as providing a pharmaceutical addition salt, such as a hydrochloride, sulfate, citrate, tartarate, mesylate, maleate, fumarate, or the like.

These salts are readily prepared by mixing a solution of equimolar amounts of the free base form of the compound and desired acid in a suitable solvent such as water, alcohol, or ether, followed by recovery of the product by collecting the precipitated salt or by evaporation of the solvent.

When used as antiarrhythmic drugs, the piperidine derivatives of the present invention may be administered by an oral or parenteral route, which may be determined depending upon age, body weight, condition of the patient. A daily dose may generally be from about 0.001 about 2000 mg/patient or animal for oral administration; in the case of parenteral administration, a daily dose may generally be from about 0.001 to about 1000 mg/patient or animal.

The piperidine derivatives of the present invention may be formulated into conventional preparation forms, for

example, tablets, powders, capsules, solutions, sugar-coated tablets or depots, which may be prepared in a conventional manner using conventional techniques. For example, tablets can be obtained by mixing a piperidine derivative of the present invention with known auxiliary substances, for example, inactive diluents (e.g. lactose, calcium carbonate or calcium phosphate), binders (e.g. gum arabic, corn starch or gelatin), sweeteners (e.g. sucrose or saccharine), flavours (e.g. peppermint, Gaultheria adenothrix oil or cherry), lubricating and wetting agents (e.g. magnesium stearate, talc or carboxymethyl cellulose).

The present invention further provides a novel antiarrhythmic agent which is a composition comprising a pharmaceutically effective amount of a piperidine derivative as defined above.

The pharmaceutical composition of the present invention is advantageous as an antiarrhythmic drug for treating mammals including humans. This can be administered perorally in the form of tablet, capsule or elixir, or parenterally in the form of a sterile solution or suspension, for the purpose of reducing or eliminating arrhythmia. The pharmaceutical composition of the present invention can be administered to patients or animals which are to be treated generally several times each in a unit dosage of from about 0.001 to about 500 mg/patient or animal, and accordingly the total dosage of the derivative may be from about 0.001 to about 2000 mg/patient or animal/day. Of course, the amount of the dosage may be varied in accordance with the condition of the disease, the weight of the patient or animal and other factors which are considered appropriate by one skilled in the art.

The above-mentioned typical combinations may be formulated as a pharmaceutical composition in a conventional manner. For example, from about 0.2 to about 500 mg of the derivative of the present invention or a pharmaceutically acceptable salt thereof or a mixture thereof is blended together with a pharmaceutically acceptable vehicle, carrier, extender, binder, antiseptic, stabilizer, flavour and the like, in an amount as required for conventional pharmaceutical preparations.

Examples of pharmaceutical additives to be used for the preparation of tablets, capsules and the like are: binders such as tragacanth, gum arabic, corn starch or gelatin; vehicles such as fine crystalline cellulose; extenders such as corn starch, pre-gelatinised starch or alginic acid; sweeteners such as sucrose, lactose or saccharin; flavours such as peppermint, an oil from Gaultheria adenothrix Maxim or cherry. When the preparation is in the form of a capsule, this may further contain a liquid carrier such as a fat and oil, in addition to the above mentioned materials. Other various materials can further be employed so as to form coated pills or to vary the physical form of the preparation by a different method. For example, tablets can be coated with shellac, sugar or both. A syrup or elixir can contain the active compound together with sucrose as a sweetener, methyl- or propyl-paraben as an antiseptic, a dye, and cherry or orange essence as a flavour.

A sterile composition for injection can be prepared in a conventional manner, for example, by dissolving or suspending the active substance in a vehicle such as distilled water for injection, together with a natural vegetable oil such as sesame oil, coconut oil, peanut oil, cotton seed oil, or a synthetic fat vehicle such as ethyl oleate. If desired, a buffer, an antiseptic, an antioxidant or the like can be incorporated into the composition.

The present invention will be further illustrated by reference to the following examples.

PREPARATION OF COMPOUNDS

Retention factor (Rf) was determined by silica gel thin layer chromatography (TLC:Merck Art 5715). Unless otherwise noted, mass spectroscopy was determined on JEOL-DX 300 by FD mode; ¹H NMR spectra were obtained in CDCl₃ with tetramethylsilane as internal standard on a Varian VXR-300 spectrometer.

"Intermediate (1)" represents 4-(5H-dibenzo[a, d]cyclohepten-5-ylidene)piperidine.

compound 1

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-[4-(N-imidazolylmethyl)cinnamyl]piperidine

To a solution of 4-(N-imidazolylmethyl)cinnamic alcohol (4.5mmol) in CHCl₃, thionyl chloride (5.4mmol) was added, and stirred for 2h at room temperature. After a usual procedure, the product was used without further purification.

The product obtained according to above-mentioned procedure was dissolved in methyl isobutyl ketone, and then intermediate (1) (4.0mmol), potassium carbonate (8.75mmol) and NaI (8.75mmol) were added to the solution, stirred at 90 °C for overnight. The mixture was washed with water, extracted with CH₂Cl₂, washed with 1 M HCl, saturated aqueous solution of NaHCO₃, and then brine, dried over MgSO₄. The solvent was evaporated at reduced pressure, the resulting mixture was purified by column chromatography (SiO₂).

MS	469(M+)
NMR	
2.2-2.4(4H,m)	2.5-2.6(2H,m)
2.8-2.9(2H,m)	3.28(2H,d)
5.07(2H,s)	6.38(1H,dt)
6.52(1H,d)	6.95(2H,s)
7.0-7.6(15H,m)	

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compound 2

1-[4-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]butanoyl]-4-hydroxypiperidine

15	TLC(CHCl ₃ : MeOH=9:1)	Rf=0.58
	MS	442(M+)
	NMR	
	1.4-1.6(2H,m)	1.8-2.0(4H,m)
20	2.1-2.2(4H,m)	2.3-2.4(4H,m)
	2.5-2.6(2H,m)	2.89(1H,m)
	3.19(1H,m)	3.7-3.8(2H,m)
	3.9-4.0(2H,m)	4.0-4.2(2H,m)
25	6.91(2H,s)	7.1-7.4(8H,m)

compound 3

30 4-[4-Dibenzo[b,e]thiepin-11(6H)-ylidene]-1-piperidinyl]-1-cyclohexylbutane

According to the practically same procedure described in preparation of compound 1,4-bromo-1-cyclohexylbutane and 4-dibenzo[b,e]thiepine-11(6H)-ylidenepiperidine were used.

35	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.74
	MS	431(M+)
	NMR	
	0.8-1.0(2H,m)	1.1-1.4(10H,m)
40	1.4-1.6(1H,m)	1.6-1.8(6H,m)
	2.1-2.4(4H,m)	2.51(2H,t)
	2.6-2.8(4H,m)	3.39(1H,d)
	4.99(1H,s)	6.9-7.1(4H,m)
45	7.2-7.4(4H,m)	

compound 4

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-nitrocinnamyl)piperidine

50 After the stepwise addition of 4-Nitrocinnamyl alcohol(5.58mmol) to a ice-cooled solution of SOCl₂(10g), the mixture was stirred for a few minutes. The residue obtained by general procedure was condensed with intermediate(1) (6.59mmol) in the presence of potassium carbonate.

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Yield 2.02mmol(36.2%)

MS

434(M+)

NMR

5	2.16-2.24(4H,m)	2.31-2.42(2H,m)
	2.60-2.68(2H,m)	3.18(2H,d)
	6.46(1H,dt)	6.55(1H,d)
	6.92(2H,s)	7.18-7.36(8H,m)
10	7.42-7.48(2H,m)	8.17-8.20(2H,m)

compound 5

- 15 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine 4-(5H-Dibenzo[a,d] cyclohepten-5-ylidene)-1-(4-nitrocinnamyl)piperidine(compound 4) was reduced by zinc in acetic acid at room temperature for 4h.

Yield 84.5%

20

MS

404(M+)

NMR

	2.20-2.42(6H,m)	2.60-3.32(4H,m)
	3.40(2H,d)	6.11(1H,dt)
25	6.43(1H,d)	6.59-6.64(2H,s)
	6.91(2H,s)	7.14-7.36(10H,m)

compound 6

30

- 1-(4-Acetylaminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine
1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) was N-acetylated by acetic anhydride using triethyl amine as base.

35 Yield 92.3%

MS

446(M+)

NMR

	2.18(3H,s)	2.20-2.55(6H,m)
40	4.70(1H,bs)	6.20(1H,dt)
	6.42(1H,d)	6.91(2H,s)
	7.15-7.36(10H,m)	7.42-7.56(2H,m)

45 compound 7

- 3-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-1-(4-nitrophenyl)propane
a) 1-Bromo-3-(4-nitrophenyl)propane

- 50 1-Bromo-3-phenylpropane(19.7mmol) was added slowly to a solution of sulfuric acid(7.4g) and nitric acid(5.4g) at ambient temperature and stirred at 60 °C. The residue (mixture of ortho and para) was purified by column chromatography on silica gel.

Yield 63.7%

55

NMR

	2.20(2H,quint.)	2.92(2H,t)
	3.40(2H,t)	7.35(2H,d)
	8.16(2H,d)	

b) compound 7

This was prepared from 1-Bromo-3-(4-nitrophenyl)propane and intermediate(1).

Yield 94.6%

MS

436(M+)

NMR

1.84(2H,m)

2.15(4H,m)

2.30(4H,m)

2.59(2H,m)

2.70(2H,t)

6.90(2H,s)

7.2-7.4(10H,m)

8.10(2H,d)

Compound 8

1-(4-Aminophenyl)-3-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]propane

3-[4-(5H-Dibennzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-1-(4-nitrophenyl)propane(compound 7) was reduced by zinc.

Yield 97.3%

MS

406(M+)

NMR

1.70(2H,m)

2.0-2.6(12H,m)

3.48(2H,br)

6.55(2H,d)

6.85(2H,s)

6.92(2H,d)

7.20(4H,m)

7.25(4H,m)

Compound 9

1-(4-Acetylaminophenyl)-3-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]propane

This was prepared from 1-(4-Aminophenyl)-3-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]propane(compound 8) and acetic anhydride.

Yield 92.9%

MS

48(M+)

NMR

1.6-1.8(4H,m)

2.15(3H,s)

2.0-2.2(2H,m)

2.2-2.4(4H,m)

2.55(4H,m)

7.1-7.4(12H,m)

compound 10

N-[3-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]propanoyl-3,4-dimethoxyanilide

MS(FAB,m/z)

481(M+)

NMR

2.25-2.36 (4H,m)

2.40-2.46 (2H,m)

2.52 (2H,t)

2.70 (2H,t)

2.68-2.80 (2H,m)

3.85 (3H,s)

3.88 (3H,s)

6.79 (2H,s)

6.93 (2H,s)

7.18-7.35 (8H,m)

7.52 (1H,s)

compound 11

4-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidiny]-1-butyl] tetrahydropyran

MS

413(M+)

NMR

1.1-1.6(10H,m)

1.7-1.8(1H,m)

2.1-2.4(8H,m)

2.5-2.6(2H,m)

3.35(2H,t)

3.93(2H,d)

6.90(2H,s)

7.2-7.4(8H,m)

compound 12

1-(N-Acetyl-4-piperidiny)-3-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidiny] propane

a) 3-(4-Piperidiny)-1-propanol

1-(4-Pyridyl)-1-propyne-3-ol was hydrogenated with rhodium on alumina as catalyst.

b) 1-Acetoxy-3-(N-acetyl-4-piperidiny)propane

This was prepared from 3-(4-Piperidiny)-1-propanol and acetic anhydride.

NMR

1.0-1.8(9H,m)

2.04(3H,s)

2.07(3H,s)

2.51(1H,t)

3.00(1H,t)

3.78(1H,br d)

4.04(2H,t)

4.58(1H,br d)

c) 3-(N-Acetyl-4-piperidiny)propanol

1-Acetoxy-3-(N-acetyl-4-piperidiny)propane was saponified by potassium carbonate.

NMR

1.0-1.2(2H,m)

1.2-1.4(2H,m)

1.4-1.8(6H,m)

2.08(3H,s)

2.53(1H,dt)

3.02(1H,dt)

3.64(2H,t)

3.79(1H,br d)

4.58(1H,br d)

d) 1-(N-Acetyl-4-piperidiny)-3-bromopropane

3-(N-Acetyl-4-piperidiny)propanol was brominated with phosphorus tribromide.

NMR

1.0-1.2(2H,m)

1.50(1H,m)

1.78(2H,quint)

2.53(1H,dt)

3.40(2H,t)

4.59(1H,br d)

1.40(2H,t)

1.74(2H,br t)

2.08(3H,s)

3.02(1H,dt)

3.80(1H,br d)

e) compound 12

Yield 77.8%

MS

440(M+)

NMR

1.0-1.2(2H,m)

1.4-1.6(3H,m)

2.05(3H,s)

2.96(1H,dt)

4.55(1H,br d)

7.2-7.4(8H,m)

1.22(2H,m)

1.68(2H,m)

2.1-2.6(11H,m)

3.74(1H,br d)

6.90(2H,s)

compound 13

5-Acetylamino-2-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]methylindan

MS

460(M+)

NMR

2.0-2.3(7H,m)

2.3-2.5(1H,m)

2.5-2.8(6H,m)

6.92(2H,s)

2.9-3.1(2H,m)

7.0-7.5(11H,m)

compound 14

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,4-dimethoxycinnamyl)piperidine

a) 4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,4-dimethoxycinnamoyl)piperidine

2,4-Dimethoxycinnamic acid(10.0mmol) and intermediate(1) was condensed by N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride.

b) compound 14

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,4-dimethoxycinnamoyl)piperidine was reduced with lithium aluminium hydride.

Yield 12.3%

MS

449(M+)

NMR

2.13-2.23(4H,m)

2.62(2H,m)

3.78(6H,s)

6.42(2H,m)

6.91(2H,s)

2.30-2.50(2H,m)

3.13(2H,d)

6.15(1H,tt)

6.68(1H,d,J=15.9Hz)

7.18-7.35(9H,m)

compound 15

1-(4-Cyanocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

a) 4-Cyanocinnamylalcohol

A Heck reaction of 4-bromobenzonitrile and acrylic acid gave 4-cyanocinnamic acid. The acid was reduced to the corresponding alcohol with ethyl chloroformate and then sodium borohydride.

Yield 78.6%

NMR

4.38(2H,dd)

6.65(1H,d)

7.40(2H,d)

6.49(1H,m)

7.44(2H,d)

b) compound 15

MS

414(M+)

NMR

2.12-2.22(4H,m)

2.52(2H,m)

6.42(2H,m)

7.18-7.35(8H,m)

7.58(2H,d)

2.30-2.42(2H,m)

3.15(2H,d)

6.92(2H,s)

7.40(2H,d)

compound 16

1-Cyclohexyl-4-[4-(10,11-dihydroxy-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]butane

A osmium tetroxide(0.4mmol) in acetone was added to the 50% aqueous solution of acetone dissolved in 1-Cyclohexyl-4-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]butane (4.8mmol) and N-methylmorpholine-N-oxide (7.2mmol). The mixture was stirred for over night at ambient temperature.

MS

445(M+)

0.7-1.4(11H,m)

2.6-3.0(8H,m)

3.26(1H,bs)

7.0-7.6(4H,m)

1.4-1.8(8H,m)

3.05(1H,bs)

5.21(2H,s)

compound 17

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-propanoylaminocinnamyl)piperidine 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) was N-acylated.

Yield 43.9%

MS

460(M+)

NMR

1.22(3H,t)

2.7-2.9(2H,m)

4.79(1H,bs)

6.43(1H,dd)

7.1-7.55(12H,m)

2.2-2.6(8H,m)

3.23(2H,d)

6.1-6.3(1H,m)

6.93(2H,s)

compound 18

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-ethoxycarbonylamino-cinnamyl)piperidine

This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine (compound 5) and ethyl chloroformate.

Yield 56.7%

MS

476(M+)

NMR

1.30(3H,t)

2.2-2.9(8H,m)

3.26(2H,dd)

4.22(2H,q)

6.1-6.3(1H,m)

6.46(1H,d)

6.67(1H,bs)

6.93(2H,s)

7.1-7.4(12H,m)

compound 19

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-methanesulfonylamino-cinnamyl)piperidine

This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine (compound 5) and methanesulfonyl chloride.

Yield 67.0%

MS

482(M+)

NMR

2.1-2.5(6H,m)

2.5-2.7(2H,m)

3.17(2H,d)

3.39(3H,s)

6.2-6.4(1H,m)

6.49(1H,d)

6.93(2H,s)

7.1-7.5(12H,m)

compound 20

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3-methoxycarbonylcinnamyl)piperidine

According to the practical same procedure of compound 16, this compound was obtained.

MS

447(M+)

NMR

2.16-2.26(4H,m)

2.30-2.44(2H,m)

2.52(2H,m)

3.14(2H,d)

3.91(3H,s)

6.38(1H,m)

6.52(1H,d)

6.92(2H,s)

7.18-7.35(9H,m)

7.52(1H,d)

7.88(1H,d)

8.01(1H,s)

compound 21

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-methoxycarbonylamino-cinnamyl)piperidine

This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine (compound 5) and methyl chloroformate.

Yield 97.5%

MS

462(M+)

NMR

2.2-2.9(8H,m)

3.10(2H,m)

3.78(3H,s)

6.2-6.4(1H,m)

6.56(1H,d)

6.72(1H,bs)

6.92(2H,s)

7.1-7.4(12H,m)

compound 22

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-pivaloylaminocinnamyl)piperidine

This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) and pivaloyl chloride.

Yield 92.0%

MS

488(M+)

NMR

1.34(9H,s)

2.2-3.2(10H,m)

6.2-6.42(1H,m)

6.55(1H,d)

6.93(2H,s)

7.1-7.44(10H,m)

7.45-7.6(2H,m)

compound 23

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-trifluoroacetylaminocinnamyl)piperidine

This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) and trifluoroacetic anhydride.

Yield 46.0%

MS

500(M+)

NMR

2.4-3.7(10H,m)

6.2-6.4(1H,m)

6.58(1H,dd)

6.93(2H,s)

7.17(2H,d)

7.2-7.45(8H,m)

7.69(2H,dd)

8.36(1H,bs)

compound 24

1-(4-Butanoylaminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) and butanoic acid.

Yield 68.5%

MS

474(M+)

NMR

5	0.99(3H,q)	1.6-1.8(2H,m)
	2.2-2.43(6H,m)	2.44-2.7(2H,m)
	2.8-3.1(2H,m)	3.35(2H,d)
	5.50(1H,bs)	6.1-6.3(1H,m)
10	6.45(1H,dd)	6.92(2H,s)
	7.1-7.4(10H,m)	7.49(2H,dd)

The following compounds were prepared according to the above-mentioned procedures.

15 compound 25

1-(4-Ethoxycarbonylamino-cinnamyl)-4-(4-fluorobenzoyl)piperidine

MS

410(M+)

20

NMR

	1.33(3H,t)	1.8-2.4(6H,m)
	3.18(2H,m)	3.43(3H,m)
25	4.21(2H,m)	6.32(1H,dt)
	6.58(1H,d)	6.6(1H,s)
	7.1-7.4(6H,m)	7.92(2H,m)

30 compound 26

4-(4-Fluorobenzoyl)-1-(4-methoxycarbonylamino-cinnamyl)piperidine

MS

396(M+)

35

NMR

	1.9-2.3(4H,m)	2.70(3H,m)
	3.28(2H,m)	3.42(3H,m)
	3.99(3H,m)	6.33(1H,dt)
40	6.58(1H,d)	6.80(1H,s)
	7.1-7.5(6H,m)	7.97(2H,m)

compound 27

45

4-(4-Fluorobenzoyl)-1-(4-propanoylamino-cinnamyl)piperidine

MS

394(M+)

50

NMR

	1.23(3H,t)	1.7-2.2(6H,m)
	2.41(2H,q)	3.1-3.5(5H,m)
	6.33(1H,dt)	6.58(1H,d)
55	7.0-7.5(7H,m)	7.98(2H,m)

compound 28

4-(4-Fluorobenzoyl)-1-(4-trifluoroacetylaminocinnamyl)piperidine

5	MS	435(M+)
	NMR	
	2.1-2.2(4H,m)	2.95-3.3(5H,m)
	3.80(2H,m)	6.25(1H,dt)
10	6.68(1H,d)	7.1-7.5(7H,m)
	7.98(2H,m)	

compound 29

1-(4-Acetylaminocinnamyl)-4-(4-fluorobenzoyl)piperidine

	MS	380(M+)
20	NMR	
	1.75-1.95(5H,m)	2.1-2.3(4H,m)
	3.0-3.3(5H,m)	6.22(1H,dt)
	6.50(1H,d)	7.05-7.55(7H,m)
25	7.98(2H,m)	

compound 30

1-(4-Aminocinnamyl)-4-(4-fluorobenzoyl)piperidine

	MS	338(M+)
	NMR	
	1.8-2.2(4H,m)	2.95-3.3(5H,m)
35	3.68(2H,m)	6.10(1H,dt)
	6.41(1H,d)	6.62(2H,m)
	7.05-7.40(6H,m)	7.97(2H,m)

40 compound 31

4-(4-Fluorobenzoyl)-1-(4-nitrocinnamyl)piperidine

45	MS	368(M+)
	NMR	
	1.8-2.2(4H,m)	3.0-3.35(5H,m)
	3.8(2H,m)	6.36(1H,dt)
50	6.57(1H,d)	7.05-7.5(6H,m)
	7.98(2H,m)	

compound 32

55 1-(4-Aminocarbonylcinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.23
	MS	432(M+)
5	compound 33	
	4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-trifluoromethylcinnamyl)piperidine	
10	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.85
	MS	457(M+)
	compound 34	
15	4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-cyanomethylcinnamyl)piperidine	
	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.89
	MS	428(M+)
20	compound 35	
	4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3,4-dichlorocinnamyl)piperidine	
25	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.72
	MS	457(M+)
	compound 36	
30	4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3,4-dimethoxy-2-nitrocinnamyl)piperidine	
	TLC(HEXANE:Ethyl acetate=1:1)	Rf=0.13
35	MS	457(M+)
	compound 37	
	4-Dibenzo[b,e]thiepin-11(6H)-ylidene-1-(4-nitrocinnamyl)piperidine	
40	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.89
	MS	454(M+)
	NMR	
45	2.1-2.3(4H,m)	2.4-2.6(2H,m)
	2.6-2.8(2H,m)	3.21(2H,d)
	3.41(1H,d)	4.98(1H,d)
	6.48(1H,dt)	6.61(1H,d)
50	7.0-7.1(4H,m)	7.2-7.4(4H,m)
	7.4-7.5(2H,m)	8.1-8.2(2H,m)
	compound 38	
55	1-(4-Aminocinnamyl)-4-dibenzo[b,e]thiepin-11(6H)-ylidenepiperidine	

TLC(CHCl₃:MeOH=9:1)R_f=0.65

MS

424(M⁺)

NMR

2.1-2.8(8H,m)

3.13(2H,d)

3.39(1H,d)

3.68(2H,bs)

4.95(1H,d)

6.08(1H,dt)

6.39(1H,d)

6.5-6.6(2H,m)

7.0-7.1(5H,m)

7.1-7.3(5H,m)

compound 39

1-(4-Acethylaminocinnamyl)-4-dibenzo[b,e]thiepin-11(6H)-ylidenepiperidine

TLC(CHCl₃:MeOH=9:1)R_f=0.58

MS

466(M⁺)

NMR

2.15(3H,s)

2.2-2.9(8H,m)

3.22(2H,d)

3.40(1H,d)

4.91(1H,d)

6.21(1H,dt)

6.48(1H,d)

7.0-7.5(13H,m)

compound 40

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,5-dimethoxycinnamyl)piperidine

TLC(CHCl₃:MeOH=9:1)R_f=0.73

MS

449(M⁺)

NMR

2.05-2.23(4H,m)

2.30-2.45(2H,m)

2.50-2.66(2H,m)

3.15(2H,d)

3.75(6H,s)

6.15(1H,m)

6.45-7.00(4H,m)

6.91(2H,s)

7.18-7.35(8H,m)

compound 41

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,3-dimethoxycinnamyl)piperidine

TLC(CHCl₃:MeOH=9:1)R_f=0.90

MS

449(M⁺)

NMR

2.1-2.2(4H,m)

2.3-2.4(2H,m)

2.5-2.7(2H,m)

3.13(2H,d)

3.77(3H,s)

3.80(3H,s)

6.28(1H,dt)

6.79(1H,d)

6.90(2H,s)

7.0-7.1(2H,m)

7.2-7.4(9H,m)

compound 42

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3,5-dimethoxycinnamyl)piperidine

5	TLC(CHCl ₃ :MeOH=9:1)	R _f =0.73
	MS	449(M ⁺)
	NMR	
	2.05-2.23(4H,m)	2.28-2.42(2H,m)
10	2.50-2.66(2H,m)	3.10(2H,d)
	3.78(6H,s)	6.10-6.42(3H,m)
	6.52(2H,m)	6.91(2H,s)
	7.18-7.35(8H,m)	

15

compound 43

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-methoxycinnamyl)piperidine

20	TLC(CHCl ₃ :MeOH=9:1)	R _f =0.87
	MS	419(M ⁺)
	NMR	
25	2.2-2.3(4H,m)	2.3-2.4(2H,m)
	2.6-2.7(2H,m)	3.15(2H,d)
	3.79(3H,s)	6.28(1H,dt)
	6.80(1H,d)	6.8-6.9(1H,m)
30	6.92(2H,s)	7.1-7.4(11H,m)

compound 44

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3-methoxycinnamyl)piperidine

35	TLC(CHCl ₃ :MeOH=9:1)	R _f =0.89
	MS	419(M ⁺)
	NMR	
40	2.1-2.2(4H,m)	2.2-2.4(2H,m)
	2.5-2.7(2H,m)	3.12(2H,d)
	3.78(3H,s)	6.23(1H,dt)
	6.42(1H,d)	6.7-6.9(4H,m)
45	6.92(2H,s)	7.2-7.4(8H,m)

compound 45

50 4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-methoxycinnamyl)piperidine

55

TLC(CHCl₃:MeOH=9:1)R_f=0.85

MS

419(M⁺)

NMR

2.1-2.2(4H,m)

2.3-2.4(2H,m)

2.6-2.7(2H,m)

3.12(2H,d)

3.79(3H,s)

6.12(1H,dt)

6.41(1H,d)

6.83(2H,d)

6.91(2H,s)

7.1-7.3(10H,m)

compound 46

4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-nitrocinnamyl)piperidine

TLC(CHCl₃:MeOH=9:1)R_f=0.93

MS

436(M⁺)

NMR

2.7-3.0(8H,m)

3.3-3.4(4H,m)

3.75(2H,d)

6.7-6.8(2H,m)

7.0-7.2(8H,m)

7.5-7.6(2H,m)

8.1-8.2(2H,m)

compound 47

1-(4-Aminocinnamyl)-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl₃:MeOH=9:1)R_f=0.64

MS

405(M⁺)

NMR

2.4-2.5(4H,m)

2.6-2.7(2H,m)

2.81(2H,dt)

3.12(2H,d)

3.3-3.4(2H,dt)

3.67(2H,bs)

6.08(1H,dt)

6.39(1H,d)

6.60(2H,d)

7.0-7.2(10H,m)

compound 48

1-(4-Acethylaminocinnamyl)-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl₃:MeOH=9:1)R_f=0.54

MS

448(M⁺)

NMR

2.4-2.6(4H,m)

2.7-2.8(8H,m)

3.21(2H,d)

6.21(1H,dt)

6.44(1H,d)

7.0-7.2(8H,m)

7.34(2H,d)

7.44(2H,d)

compound 49

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-fluorocinnamyl)piperidine

TLC(CHCl₃:MeOH=9:1)R_f=0.88

MS

445(M⁺)

NMR

2.1-2.2(4H,m)

2.3-2.4(2H,m)

2.6-2.8(2H,m)

3.09(2H,d)

6.17(1H,dt)

6.42(1H,d)

6.87(2H,s)

6.9-7.0(2H,m)

7.2-7.3(10H,m)

compound 50

3-[4-(5H-Dibenzo [a,d]cyclohepten-5-ylidene)-1-piperidinyl]-1-(3-pyridyl)-1-propene

TLC(CHCl₃:MeOH 9:1) R_f=0.44

MS

390(M⁺)

NMR

2.1-2.2(4H,m)

2.3-2.5(2H,m)

2.55-2.65(2H,m)

3.09(2H,d)

6.31(1H,dt)

6.43(1H,d)

6.90(2H,s)

7.1-7.3(9H,m)

7.62(1H,d)

8.41(1H,dd)

8.54(1H,d)

compound 51

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-hydroxycinnamyl)piperidine

TLC(CHCl₃:MeOH=9:1)R_f=0.55

MS(FAB.m/z)

406(MH⁺)

NMR

2.1-2.3(4H,m)

2.3-2.5(2H,m)

2.6-2.8(2H,m)

3.07(2H,d)

5.97(1H,dt)

6.37(1H,d)

6.63(2H,d)

6.87(2H,s)

7.0-7.3(11H,m)

compound 52

1-(4-Acetoxycinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl₃:MeOH= 9:1)R_f=0.87

MS

447(M⁺)

NMR

2.1-2.2(4H,m) 2.29(3H,s)

2.3-2.4(2H,m)

2.6-2.7(2H,m)

3.12(2H,d)

6.21(1H,dt)

6.43(1H,d)
6.9-7.0(2H,m)

6.92(2H,s)
7.2-7.4(10H,m)

5

compound 53

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-hydroxy-3-methoxycinnamyl)piperidine

10

TLC(CHCl₃:MeOH=9:1)R_f=0.87

MS

435(M⁺)

NMR

15

2.1-2.2(4H,m)

2.3-2.4(2H,m)

2.6-2.7(2H,m)

3.08(2H,d)

3.81(3H,s)

6.09(1H,dt)

6.39(1H,d)

6.78(1H,s)

6.8-6.9(2H,m)

6.87(2H,s)

20

7.1-7.3(9H,m)

compound 54

1-(4-Acetoxy-3-methoxycinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

25

TLC(CHCl₃:MeOH=9:1)R_f=0.83

MS

477(M⁺)

NMR

30

2.1-2.2(4H,m)

2.29(3H,s)

2.3-2.4(2H,m)

2.6-2.7(2H,m)

3.09(2H,d)

3.81(3H,s)

6.08(1H,dt)

6.38(1H,d)

35

6.80(2H,s)

6.9-7.4(11H,m)

7.2-7.4(9H,m)

compound 55

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3-hydroxycinnamyl)piperidine

45

TLC(CHCl₃:MeOH=9:1)R_f=0.45

MS

405(M⁺)NMR(CD₃OD)

2.10-2.30(4H,m)

2.31-2.50(2H,m)

2.70(2H,m)

3.16(2H,d)

6.42(1H,m)

6.70(1H,m)

50

6.84-6.95(2H,m)

6.95(2H,s)

7.10-7.38(10H,m)

compound 56

1-(3-Acetoxy-3-methoxycinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl₃:MeOH=9:1) R_f=0.80

MS 447(M⁺)

NMR

2.13-2.24(4H,m) 2.30-2.45(2H,m)

2.62(2H,m)

3.14(2H,d)

6.28(1H,m)

6.43(1H,d)

6.92(2H,s)

6.92-6.97(1H,m)

7.04(1H,s)

7.18-7.35(10H,m)

compound 57

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-[3-(2-methoxyacethoxy)cinnamyl] piperidine

TLC(CHCl₃:MeOH=9:1)

R_f=0.65

MS

477(M⁺)

NMR(hydrochloride)

2.21-2.40(2H,m)

2.48-2.60(4H,m)

2.92-3.15(2H,m)

3.20-3.65(2H,m)

3.54(3H,s)

4.26(2H,s)

6.40-6.60(2H,m)

6.92(2H,s)

7.00-7.39(12H,m)

compound 58

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-methoxycarbonylcinnamyl)piperidine

TLC(CHCl₃:MeOH=9:1)

R_f=0.55

MS

447(M⁺)

NMR

2.52-2.68(4H,m)

2.92-3.10(2H,m)

3.30-3.50(2H,m)

3.62(2H,d)

6.42(1H,dt)

6.91(2H,s)

7.18(1H,d)

7.24-7.40(8H,m)

7.42-7.60(3H,m)

7.90-7.95(1H,m)

compound 59

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-methoxycarbonylcinnamyl)piperidine

TLC(CHCl₃:MeOH=9:1)

R_f=0.50

MS

447(M⁺)

NMR

2.15-2.24(4H,m)

2.32-2.45(2H,m)

2.60-2.68(2H,m)

3.16(2H,d)

3.90(3H,s)

6.39(1H,dt)

6.50(1H,d)

6.92(2H,s)

7.20-7.36(8H,m)

7.37-7.41(2H,m)

7.96-8.00(1H,m)

compound 60

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3-methoxy-2-nitrocinnamyl)piperidine

5 TLC(HEXANE:EtOAc=1:1) Rf=0.30

MS

464(M+)

NMR

10 2.1-2.23(3H,m) 2.24-2.42(2H,m)
 2.43-2.7(3H,m) 3.07(2H,d)
 3.81(3H,s) 6.37(2H,s)
 6.8-7.0(3H,m) 7.05-7.4(10H,m)

15

compound 61

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-ethoxycarboxycinnamyl)piperidine

20 TLC(CHCl3:MeOH=9:1) Rf=0.83

MS

477(M+)

NMR

25 1.23(3H,t) 2.1-2.2(4H,m)
 2.3-2.4(2H,m) 2.5-2.7(2H,m)
 3.13(2H,d) 4.18(2H,q)
 6.24(1H,d) 6.43(1H,d)
 6.90(2H,s) 7.0-7.1(2H,m)
 30 7.1-7.4(10H,m)

30

compound 62

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-methoxyacethoxycinnamyl)piperidine

35 TLC(CHCl3:MeOH=9:1) Rf=0.75
 MS 477(M+)

NMR

40 2.0-2.2(4H,m) 2.4-2.6(2H,m)
 2.5-2.7(2H,m) 3.17(2H,d)
 3.52(3H,s) 4.24(2H,s)
 6.22(1H,dt) 6.44(1H,d)
 45 6.95(2H,s) 7.0-7.4(12H,m)

45

compound 63

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3,4-dihydroxycinnamyl)piperidine

50

55

	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.35
	MS(FAB.m/z)	422(M+)
	NMR	
5	2.0-2.3(4H,m)	2.4-2.6(2H,m)
	2.6-2.8(2H,m)	3.17(2H,dt)
	6.27(1H,dt)	6.41(1H,d)
	6.87(2H ,s)	6.9-7.5(13H,m)
10	compound 64	
	4-Dibenzo[b,e]thiepin-11(6H)-ylidene-1-(2,4-dimethoxycinnamyl)piperidine	
15	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.75
	MS	469(M+)
	compound 65	
20	4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,4-dimethoxycinnamyl)piperidine	
	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.71
25	MS	451(M+)
	compound 66	
	1-(4-Aminosulfonylcinnamyl)-4-dibenzo[b,e]oxepin-11(6H)-ylidenepiperidine	
30	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.32
	MS	475(M+)
35	compound 67	
	1-(4-Aminosulfonylcinnamyl)-4-(9-thioxanthylidene)piperidine	
40	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.35
	MS	475(M+)
	compound 68	
45	1-(4-Aminosulfonylcinnamyl)-4-(9-xanthylidene)piperidine	
	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.31
50	MS	458 (M+)
	compound 69	
	1-(4-Aminosulfonylcinnamyl)-4-diphenylmethylenepiperidine	
55	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.31
	MS	444(M+)

compound 70

1-(4-Aminosulfonylcinnamyl)-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

5

TLC(CHCl₃:MeOH=9:1)
MSR_f=0.34
471(M⁺)

compound 71

10

1-(4-Aminosulfonyl- α -methylcinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

15

TLC(CHCl₃:MeOH=9:1)
MSR_f=0.29
483(MH⁺)

compound 72

20

1-(4-Aminosulfonyl- β -methylcinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidineTLC(CHCl₃:MeOH=9:1)
MSR_f=0.45
483(MH⁺)

25

compound 73

1-(2-Chlorobenzyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

30

MS
H-NMR
2.1-2.8(8H,m)
6.90(2H,s)397(M⁺)

3.63(2H,bs)
7.1-7.3(12H,m)

35

compound 74

1-Cyclohexyl-3-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]propane

40

MS
H-NMR
0.8-2.1(15H,m)
2.68(2H,d)
3.0(2H,dd)
6.94(2H,s)397(M⁺)

2.47(2H,dd)
2.7-2.9(2H,m)
3.49(2H,d)
7.1-7.4(8H,m)

45

compound 75

50

1-Cyclohexyl-4-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]butane

55

	MS	411(M+)
	H-NMR	
	0.8-2.1(15H,m)	2.47(2H,dd)
5	2.68(2H,d)	2.7-2.9(2H,m)
	3.0(2H,dd)	3.49(2H,d)
	6.92(2H,s)	7.1-7.4(8H,m)

10 compound 76

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-hexylpiperidine

15	Yield 95.6%	
	TLC(CHCl ₃ : MeOH=9:1)	Rf=0.68
	MS	357(M+)
	H-NMR(CDCl ₃)	
20	0.85(3H,d,J=8Hz)	1.2-1.4(6H,m)
	1.7-1.9(2H,m)	2.31(2H,dd,J=12,8Hz)
	2.53(2H,d,J=12Hz)	2.7-2.8(2H,m)
	3.14(2H,td,J=8,3Hz)	3.40(2H,d,J=12Hz)
25	6.92(2H,s)	7.2-7.4(8H,m)

compound 77

1-Decyl-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

30	Yield 66.7%	
	TLC(CHCl ₃ :MeOH=9:1)	Rf=0.75
	MS	413(M+)
35		
	NMR(hydrochloride)	
	0.85(3H,t,J=8Hz)	1.2-1.4(14H,m)
40	1.7-1.9(2H,m)	2.33(2H,dd,J=12,8Hz)
	2.54(2H,d,J=12Hz)	2.7-2.8(2H,m)
	3.15(2H,td,J=8,3Hz)	3.39(2H,d,J=12Hz)
	6.92(2H,s)	7.1-7.4(8H,m)

45

compound 78

5-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-2-(3,4-dichlorophenyl)-2-isopropylvaleronitrile

50

55

Yield 69.1%

TLC(CHCl₃: MeOH=9:1)R_f=0.60

MS

542(M⁺)H-NMR(CDCl₃)

0.77(3H,d,J=8Hz)

1.18(3H,d,J=8Hz)

2.0-3.4(15H,m)

6.90(2H,s)

7.18(H,dd,J=9,2Hz)

7.2-7.4(8H,m)

7.48(1H,d,J=9Hz)

7.53(1H,s)

compound 79

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-[3-[2-(cinnamoylamino)phenylthio]-1-propyl]piperidine

TLC(CHCl₃:MeOH=9:1)R_f=0.66

MS

568(M⁺)H-NMR(CDCl₃)

1.73(2H,tt,J=7,7Hz)

2.0-2.2(4H,m)

2.3-2.4(2H,m)

2.38(2H,t,J=7Hz)

2.5-2.6(2H,m)

2.78(2H,t,J=7Hz)

6.59(1H,d,J=16Hz)

6.88(2H,s)

7.08(1H,tt,J=8,1Hz)

7.1-7.4(12H,m)

7.5-7.6(3H,m)

7.76(1H,d,J=16Hz)

8.55(1H,d,J=8Hz)

8.78(1H,bs,NH)

compound 80

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-cinnamylpiperidine

TLC(CHCl₃: MeOH=9:1)R_f=0.69

MS

389(M⁺)H-NMR(CDCl₃)

2.1-2.3(4H,m)

2.4-2.5(2H,m)

2.6-2.7(2H,m)

3.14(2H,d,J=7Hz)

6.26(2H,dt,J=16,7Hz)

6.48(2H,d,J=16Hz)

6.92(2H,s)

7.1-7.4(8H,m)

compound 81

5-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-2,2-diphenylvaleronitrile

Yield 57.7%

TLC(CHCl₃: MeOH=9:1)R_f=0.74

MS

506(M⁺)H-NMR(CDCl₃)

1.5-1.7(2H,m)

2.0-2.2(4H,m)

2.3-2.6(8H,m)

6.87(2H,s)

7.1-7.4(18H,m)

compound 82

5-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-2-(3-trifluoromethylphenyl)-2-isopropylvaleronitrile

5

Yield 47.5%

TLC(CHCl₃: MeOH=9:1)R_f=0.75

MS

540(M⁺)

10

H-NMR(CDCl₃)

0.76(3H,d,J=7Hz)

1.0-1.2(1H,m)

1.5-1.6(1H,m)

1.9-2.5(13H,m)

6.88(2H,s)

7.1-7.3(8H,m)

15

7.48(1H,d,J=8Hz)

7.56(1H,d,J=8Hz)

7.59(1H,s)

compound 83

20

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-fluorobenzyl)piperidine

TLC(CHCl₃: MeOH=9:1)R_f=0.75

MS

381(M⁺)

25

H-NMR(CDCl₃)

2.1-2.2(4H,m)

2.3-2.4(2H,m)

2.5-2.6(2H,m)

3.53(2H,s)

6.88(2H,s)

6.96(1H,dd,J=8,8Hz)

30

7.04(1H,dd,J=7,7Hz)

7.1-7.4(10H,m)

compound 84

35

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-fluorophenylethyl)piperidine

TLC(CHCl₃: MeOH=9:1)R_f=0.55

MS

395(M⁺)H-NMR(CDCl₃)

40

2.1-2.8(12H,m)

6.9-7.4(2H,m)

compound 85

45

5-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-2-(3-trifluoromethylphenyl)valeronitrile

TLC(CHCl₃: MeOH=9:1)R_f=0.56

MS

498(M⁺)H-NMR(CDCl₃)

50

1.5-2.7(14H,m)

3.97(1H,t,J=7Hz)

6.90(2H,s)

7.1-7.6(12H,m)

compound 86

55

1-(3-Aminobenzyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl₃: MeOH=9:1)R_f=0.62

MS

378(M⁺)H-NMR(CDCl₃)

2.1-2.8(8H,m)

3.50(2H,s)

3.4-3.8(2H,bs)

6.5-6.8(2H,m)

6.93(2H,s)

7.0-7.4(10H,m)

compound 87

4-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-3',4'-dimethoxybutyrophenone

TLC(CHCl₃: MeOH=9:1)R_f=0.52

MS

479(M⁺)H-NMR(CDCl₃)

1.8-2.6(12H,m)

2.95(2H,t,J=8Hz)

3.93(3H,s)

3.96(3H,s)

6.85(1H,d,J=10Hz)

6.88(2H,s)

7.2-7.4(8H,m)

7.5-7.7(2H,m)

compound 88

1-(4-Cyanobenzyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidine

TLC(CHCl₃:MeOH=9:1)R_f=0.70

MS(FD.m/z)

388(M⁺)

H-NMR

2.2-2.5(2H,m)

2.5-2.8(2H,m)

3.0-3.4(4H,m)

4.03(2H,d)

6.92(2H,s)

7.1-8.0(12H,m)

compound 89

1-Cyclohexyl-4-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]butane

TLC(HEXANE.:EtOAc=1:1)

R_f=0.67

MS

413(M⁺)

H-NMR

0.80-0.88(2H,m)

1.10-1.73(15H,m)

2.12-2.19(2H,m)

2.28-2.30(2H,m)

2.32-2.47(4H,m)

2.64-2.69(2H,m)

2.77-2.86(2H,m)

3.36-3.45(2H,m)

7.05-7.15(8H,m)

compound 90

Cyclohexyl-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]methane

TLC(CHCl₃:MeOH=9:1)R_f=0.58

MS(FD.m/z)	369(M+)
H-NMR	
0.7-2.9(20H,m)	6.91(2H,s)
7.05-7.4(8H,m)	

5

compound 91

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,3-dimethoxybenzyl)piperidine

10

TLC(CHCl ₃ :MeOH=9:1)	R _f =0.63
MS(FD.m/z)	423(M+)
H-NMR	
2.0-2.8(10H,m)	3.80(3H,s)
3.84(3H,s)	6.7-7.4(11H,m)
6.89(2H,s)	

15

20 compound 92

3-Cyanopropyl-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

NMR

25

1.62-2.72(14H,m)	6.92(2H,s)
7.10-7.30(8H,m)	

compound 93

30

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3,4-dimethoxyphenacyl)piperidine

MS 451(M+)

NMR

35

2.15-2.30(4H,m)	2.37-2.45(2H,m)
2.65-2.75(2H,m)	3.70(2H,s)
3.90(3H,s)	3.92(3H,s)
6.85(1H,d)	6.90(2H,s)
7.18-7.34(8H,m)	7.59(1H,d)
7.66(1H,dd)	

40

compound 94

45

1-Cyclohexyl-6-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]hexane

TLC(CHCl₃:MeOH=9:1) R_f=0.65

MS(FD.m/z) 439(M+)

50

H-NMR

0.8-1.0(2H,m)	1.1-1.4(10H,m)
1.5-1.7(8H,m)	2.2-2.4(1H,m)
2.5-2.9(5H,m)	3.0-3.2(2H,m)
3.4-3.6(3H,m)	6.92(2H,s)
7.1-7.4(8H,m)	

55

compound 95

1-(4-Cyclohexylbutyl)-4-(9-thioxanthylidene)piperidine

5

TLC(CHCl₃: MeOH=9:1)R_f=0.69

MS(FD.m/z)

417(M⁺)

H-NMR

10

0.8-1.0(2H,m)

1.1-1.4(9H,m)

1.5-1.7(6H,m)

2.2-2.4(2H,m)

2.5-2.6(2H,m)

2.8-2.9(2H,m)

2.9-3.1(6H,m)

7.1-7.5(8H,m)

15

compound 96

1-(4-Cyclohexylbutyl)-4-(9-xanthylidene)piperidine

20

TLC(CHCl₃: MeOH=9:1)R_f=0.74

H-NMR

0.8-1.0(2H,m)

1.1-1.4(9H,m)

1.5-1.7(6H,m)

2.3-2.4(2H,m)

25

2.52(4H,t)

2.91(4H,t)

7.0-7.4(8H,m)

compound 97

30

5-[4-(4-Fluorobenzoyl)-1-piperidinyl]-2-isopropyl-2-(3,4,5-trimethoxyphenyl)valeronitrile

TLC(CHCl₃: MeOH=9:1)R_f=0.56

MS

497(M⁺)

35

H-NMR(CDCl₃)

0.76(3H,bs)

1.0-1.2(1H,m)

1.16(3H,bs)

1.4-2.5(12H,m)

2.9-3.4(3H,m)

3.82(3H,s)

40

3.87(3H,s)

6.6-6.8(2H,m)

6.6-6.8(2H,m)

7.0-7.2(2H,m)

7.8-8.1(2H,m)

45

compound 98

2-(3,4-Dimethoxyphenyl)-2-dodecyl-5-[4-(4-fluorobenzoyl)-1-piperidinyl]valeronitrile

50

55

TLC(CHCl₃: MeOH=9:1)R_f=0.70

MS

592(M⁺)H-NMR(DMSO-d₆)

5	0.84(3H,t,J=8Hz)	1.2-1.5(22H,m)
	1.8-2.1(8H,m)	2.9-3.1(4H,m)
	3.4-3.5(2H,m)	3.6-3.8(1H,m)
	3.76(3H,s)	3.79(3H,s)
10	6.9-7.0(3H,m)	7.40(2H,dd,J=8,8Hz)
	8.07(2H,dd,J=10,8Hz)	

compound 99

15 5-[4-(3,4-Dimethoxybenzoyl)-1-piperidiny]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile

TLC(CHCl₃: MeOH=9:1)R_f=0.83

MS

508(M⁺)20 H-NMR(CDCl₃)

	0.80(3H,t,J=6Hz)	1.21(3H,t,J=6Hz)
	2.0-3.8(16H,m)	3.89(3H,s)
	3.93(3H,s)	3.96(6H,s)
25	6.86(1H,d,J=8Hz)	6.91(1H,d,J=8Hz)
	6.94(1H,d,J=2Hz)	7.00(1H,dd,J=8,2Hz)
	7.44(1H,d,J=2Hz)	7.49(1H,dd,J=8,2Hz)

30 compound 100

5-[4-[Bis(4-fluorophenyl)methylene]-1-piperidiny]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile

TLC(CHCl₃: MeOH=9:1)R_f=0.54

MS

544(M⁺)H-NMR(CDCl₃)

35	0.78(3H,d,J=8Hz)	1.20(3H,d,J=8Hz)
	1.6-3.6(15H,m)	3.87(3H,s)
40	3.94(3H,s)	6.8-7.1(11H,m)

compound 101

45 2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-[4-(2,4,6-trimethylbenzoyl)-1-piperidiny]valeronitrile

TLC(CHCl₃: MeOH=9:1)R_f=0.64

MS

490(M⁺)50 H-NMR(CDCl₃)

	0.8-1.3(6H,m)	1.9-3.6(25H,m)
	3.9-4.0(6H,m)	6.8-7.0(5H,m)

55 compound 102

2-(3,4-Dimethoxyphenyl)-5-[4-(4-fluorobenzoyl)-1-piperaziny]-2-isopropylvaleronitrile

TLC(CHCl₃: MeOH=9:1)R_f=0.70

MS

421(M⁺)H-NMR(CDCl₃)

5

0.81(3H,d,J=7Hz)

1.22(3H,d,J=7Hz)

1.5-1.7(2H,m)

2.15(1H,qq,J=7,7Hz)

2.2-2.5(2H,m)

3.0-3.6(10H,m)

3.89(3H,s)

3.95(3H,s)

10

6.88(2H,d,J=8Hz)

6.95(2H,d,J=2Hz)

7.04(2H,dd,J=8,2Hz)

7.1-7.2(3H,m)

7.37(2H,dd,J=8,8Hz)

15

compound 103

5-[4-(4-Fluorobenzoyl)-1-piperidiny]-2-phenylvaleronitrile

20

TLC(CHCl₃:MeOH=9:1)R_f=0.54

MS

364(M⁺)H-NMR(CDCl₃)

25

1.6-1.8(2H,m,)

1.8-1.9(4H,m)

1.9-2.0(2H,m)

2.0-2.2(2H,m)

2.41(2H,t,J=7Hz)

2.9-3.0(2H,m)

3.20(1H,m)

3.88(1H,t,J=7Hz,)

30

7.1-7.2(2H,m)

7.3-7.4(5H,m,)

7.9-8.0(2H,m)

compound 104

35

2-(3,4-Dimethoxyphenyl)-5-[4-(4-fluorophenyl)methylene-1-piperidiny]-2-isopropylvaleronitrile

TLC(CHCl₃: MeOH=9:1)R_f=0.73

MS

450(M⁺)

40

H-NMR(CDCl₃)

0.80(3H,d,J=8Hz)

1.20(3H,d,J=8Hz)

1.5-3.6(15H,m)

3.9-4.0(6H,m)

6.4-6.5(1H,m)

6.8-7.2(7H,m)

45

compound 105

2-Butyl-2-(3,4-dimethoxyphenyl)-5-[4-(4-fluorobenzoyl)-1-piperidiny]valeronitrile

50

55

TLC(CHCl₃:MeOH=9:1)R_f=0.67

MS

480(M⁺)H-NMR(CDCl₃)

5	0.86(3H,t,J=8Hz)	1.0-3.8(21H,m)
	3.88(3H,s)	3.96(3H,s)
	6.87(1H,d,J=8Hz)	6.92(1H,s)
	6.99(1H,d,J=8Hz)	7.18(2H,dd J=8,8Hz)
10	7.92(2H,dd J=8.6Hz)	

compound 106

5-[4-(4-Fluorobenzoyl)-1-piperidiny]-2-isopropyl-2-(1-methylpyrrole-2-yl)valeronitrile

15

TLC(CHCl₃: MeOH=9:1)R_f=0.54

MS

409(M⁺)H-NMR(CDCl₃)

20	1.00(3H,d,J=7Hz)	1.08(3H,d,J=7Hz)
	1.4-1.5(1H,m,CH ₂ CCN)	1.5-1.7(1H,m,CH ₂ CCN)
	1.7-1.9(4H,m)	1.9-2.1(4H,m)
	2.24(1H,hept J=7Hz)	2.3-2.4(2H,m)
25	2.8-2.9(2H,m)	3.18(1H,pseud hept.)
	3.74(3H,s)	6.00-6.03(1H,m)
	6.10-6.14(1H,m)	6.52-6.54(1H,m)
	7.09-7.16(1H,m)	7.93-7.98(2H,m)

30

compound 107

[2-(2-Nitrobenzenesulfonyl)aminoethyl]-4-(4-fluorobenzoyl)piperidine

35

MS(FAB,m/z)

436(MH⁺)

NMR

	1.80-2.05(5H,m)	3.04-3.35(6H,m)
40	3.56-3.65(2H,m)	3.65-3.75(1H,m)
	7.90-7.95(2H,m)	7.40(2H,dd J=8,8Hz)
	8.45(1H,bs)	8.02-8.13(4H,m)

45

compound 108

2-(3,4-Dimethoxyphenyl)-5-[4-(4-fluorobenzoyl)-1-piperidiny]valeronitrile

50

MS(m/z)

424(M⁺)

NMR

	1.8-2.4(8H,m)	2.9-3.7(6H,m)
	3.85(3H,s)	3.88(3H,s)
55	3.8-4.4(2H,m)	6.8-6.9(3H,m)
	7.1-7.2(2H,m)	7.9-8.0(2H,m)

compound 109

1-[2-(2-Ethoxycarbonylamino benzenesulfonyl)aminoethyl]-4-(4-fluorobenzoyl)piperidine

5	MS(FAB.m/z)	478(MH ⁺)
	NMR	
	1.12(3H,t,J=8Hz)	1.82-2.10(5H,m)
	3.12-3.27(2H,m)	3.65-3.77(4H,m)
10	4.10(2H,q,J=8Hz)	4.23-4.30(2H,m)
	6.16(1H,br)	6.68(1H,ddJ=8,8Hz)
	6.89(1H,d,J=8Hz)	7.36(1H,ddJ=8,8Hz)
	7.40(2H,dd,J=8,6Hz)	7.59(1H,d,J=8Hz)
15	8.10(2H,ddJ=8,6Hz)	

compound 110

Methyl 2-[N-methyl-N-2-[2,4(1H,3H)-quinazolinedione-3-yl]-ethylamino]ethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

	MS	578(MH ⁺)
	NMR	
25	2.30(3H,s)	2.34(3H,s)
	2.38(3H,s)	2.60-2.95(6H,m)
	3.83(3H,s)	4.08(2H,t,J=7Hz)
	4.04(1H,s)	5.86(1H,s)
30	6.91(1H,dd,J=8,8Hz)	7.08(1H,ddJ=8,8Hz)
	7.23(1H,dd,J=8,8Hz)	7.48(1H,ddJ=8,8Hz)
	7.70(1H,d,J=8Hz)	7.85(1H,d,J=8Hz)
	8.02(1H,s)	

compound 111

1,3-Bis[4-(4-fluorobenzoyl)piperidine-1-yl]propane

40	NMR	
	1.65-2.22(12H,m)	2.25-3.33(12H,m)
	7.02(4H,dd,J=8,8Hz)	7.88(4H,dd,J=8,6Hz)

compound 112

2-(3,4-Dimethoxyphenyl)-5-[4-(a-hydroxy-4-fluorobenzyl)-1-piperidinyl]-2-isopropylvaleronitrile

50

55

MS

469

NMR

0.78(3H,dd,J=7Hz)

1.1-1.2(4H,m)

1.16(3H,d,J=7Hz)

1.2-1.4(1H,m)

1.4-1.6(2H,m)

1.6-1.9(4H,m)

2.0-2.1(2H,m)

2.19(2H,pseud t,J=8Hz)

2.6-2.9(2H,m)

3.86(3H,s)

3.87(3H,s)

4.26(1H,d,J=7Hz)

6.8-7.1(5H,m)

7.1-7.3(2H,m)

compound 113

2,2-Diphenyl-5-[4-(4-fluorobenzoyl)-1-piperidiny]valeronitrile

NMR

1.9-2.1(4H,m)

3.0-3.1(4H,m)

3.2-3.3(2H,m)

3.7-3.8(1H,m)

7.18(2H,dd,J=8,8Hz)

7.2-7.5(10H,m)

7.92(2H,dd,J=10,8Hz)

compound 114

2-(3,4-Dimethoxyphenyl)-5-[4-(4-fluorobenzoyl)-1-piperidiny]-2-octylvaleronitrile

MS

536(M+)

NMR

0.86(3H,d,J=8Hz)

1.0-3.8(14H,m)

3.88(3H,s)

3.96(3H,s)

6.87(1H,d,J=8,2Hz)

6.92(1H,d,J=2Hz)

6.99(1H,dd,J=8,2Hz)

7.18(2H,dd,J=8,8Hz)

7.90(2H,dd,J=10,8Hz)

compound 115

4-(4-Fluorobenzoyl)-1-[2-(N-phenylcarbamoylamino)ethyl]piperidine

MS

369(M+)

EXAMPLESEvaluation of antiarrhythmic activity of the compounds

Example 1

Female Guinea Pigs, weighing 250-350g, were anesthetized with urethane. The lead II ECG was continuously recorded.

Drugs, compound 1 and compound 2, were dissolved in the 2.5% nicot 2.5% ethanol solution, and injected into the femoral vein.

After 30min of drug injection ouabain was infused intravenously through the left femoral vein at a rate of 10ug/kg/min.

The time, ventricular premature contractions (VPC) ventricular fibrillation (VF) and cardiac arrest (CA) appeared on ECG, were measured, and the cumulative ouabain dosage to induce ventricular premature contractions,

ventricular fibrillation and cardiac arrest, respectively, was calculated.

The results are summarized in Table 1.

Example 2

5

Mongrel dogs of either sex, weighing 8-20 kg, were anesthetized with pentobarbitone sodium, 30mg/kg. The lead II ECG, atrial electrogram from catheter tip electrodes in the right atrium, and blood pressure were continuously recorded. Ouabain 40 ug/kg was injected intravenously and with an additional 10 ug/kg every 20 min until stable ventricular arrhythmias were produced. The severity of arrhythmia was expressed by the arrhythmic ratio i.e. number of ventricular ectopic beats divided by the total heart rate. The arrhythmic ratio was calculated for 60 min after bolus intravenous administration.

10

The results are summarized in Table 2.

Example 3

15

Mongrel dogs of either sex, weighing 8-20 kg, were anaesthetized initially with thiopentone sodium. After incubation, 1.0% halothane, vaporized with 100% O₂, was administered with volume limited ventilator. Adrenaline was infused through the left femoral vein at the rate of 2.5-5 ug/kg/min. After 3 min of adrenaline infusion, drugs were injected into the right femoral vein. The lead II ECG, atrial electrogram from catheter tip electrodes in the right atrium and blood pressure were continuously recorded. The severity of ectopic beats divided by the total heart rate. The arrhythmic ratio was calculated for 15 min after drug administration.

20

The results are summarized in Table 3.

Example 4

25

Three mice were subjected to one group experiment. Drugs were administered with intraperitoneal injection in three mice 30min before deep chloroform anaesthesia. If less than two mice displayed cardiac arrhythmia or tachycardia, above 200 beats/min, when exposed to deep chloroform anaesthesia, the drug was judged as having an antiarrhythmic effect.

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The results are summarized in Table 4.

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50

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TABLE 1

	Compound #	Dose (mg/kg)	VPC (μ g/kg)	VF (μ g/kg)	CA (μ g/kg)
5	control		153	221	324
	9	1	169	236	294
	10	1	166	245	304
10	11	1	163	256	304
	13	1	169	253	299
	14	1	144	333	416
	16	1	172	217	273
	17	1	184	275	380
15	18	1	203	330	395
	20	1	181	366	420
	21	1	163	334	393
	22	1	178	346	409
20	23	0.3	142	442	499
	24	1	168	250	306
	25	1	155	269	326
	27	1	163	255	309
25	28	1	150	291	348
	29	1	159	288	344
	30	1	145	279	358
	31	1	113	271	349
	32	1	212	308	374
30	33	1	152	606	646
	34	1	125	556	579
	35	1	159	342	413
	36	1	149	344	399
35	37	1	160	298	368
	38	1	175	357	427
	39	1	254	334	422
	40	1	170	321	372
	41	1	152	295	357
40	42	1	225	386	454
	43	1	203	372	469
	44	3	205	617	656
	45	1	147	335	389
45	46	1	180	347	431
	47	1	240	265	351
	48	1	212	247	334
	49	1	140	311	380
50	51	1	146	259	344
	52	3	205	441	476
	53	3	202	398	458
	54	1	193	264	350
	55	1	175	320	374
55	56	3	187	254	309
	57	1	136	280	346
	58	3	174	384	448

TABLE 1 (continued)

	Compound #	Dose (mg/kg)	VPC (μ g/kg)	VF (μ g/kg)	CA (μ g/kg)
5	59	1	203	367	419
	60	1	186	534	586
	61	1	232	294	356
10	62	1	186	389	454
	63	1	211	322	398
	64	1	121	309	365
	65	1	146	325	381
	66	3	164	264	312
15	67	3	155	193	245
	69	3	185	202	274
	70	1	153	373	432
	72	1	171	282	363
20	74	1	182	239	289
	75	1	178	257	305
	76	1	196	205	274
	77	1	179	310	369
	78	1	154	279	337
25	79	1	172	302	358
	80	1	200	329	383
	81	1	183	267	329
	82	1	160	285	339
30	83	1	176	261	305
	84	1	168	277	335
	85	1	184	270	318
	86	1	162	240	292
35	87	1	199	260	305
	88	1	185	254	318
	89	1	204	257	312
	90	1	178	228	273
	91	1	169	286	338
40	94	1	178	301	357
	95	1	174	264	305
	96	1	178	264	312
	97	1	134	332	397
45	98	1	160	318	370
	100	1	185	275	355
	101	1	161	221	293
	102	1	163	246	297
	103	1	184	308	351
50	104	1	168	244	311
	106	1	199	312	362

55

TABLE 2

time after administration (min)	Arrhythmic Ratio	
	Compound # 23 30ug/kg	Compound #75 300ug/kg
0	1.00	1.00
2	1.00	0.80
4	1.00	0.71
6	0.60	0.41
8	0.77	0.19
10	0.50	0.19
12	0.50	0.43
15	0.50	0.43
20	0.00	0.38
30	0.00	0.45
60	0.00	0.45

TABLE 3

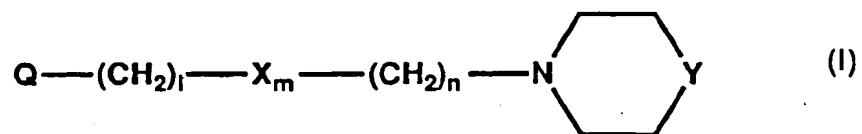
time after administration (min)	Arrhythmic Ratio	
	Compound #23 10ug/kg	Compound #75 300ug/kg
0	1.00	1.00
2	0.80	0.66
4	0.50	0.41
6	0.00	0.18
8	0.00	0.08
10	0.00	0.07
12	0.00	0.07
15	0.00	0.00

TABLE 4

Compound #	minimam effective dose (mg/kg)
107	100
108	50
109	100
110	100
111	100
112	100
113	10
114	25
115	50

Claims

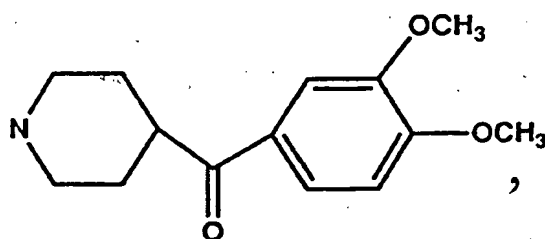
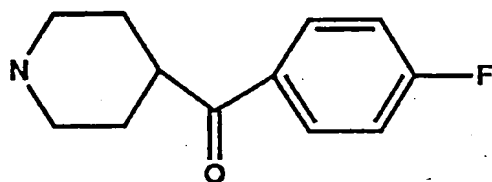
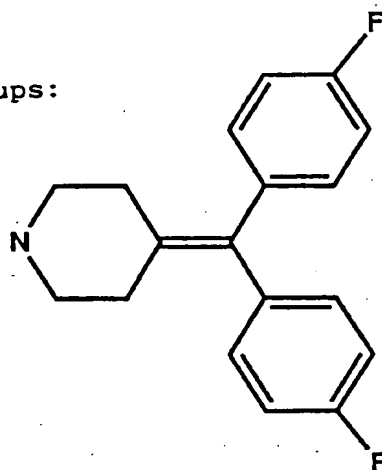
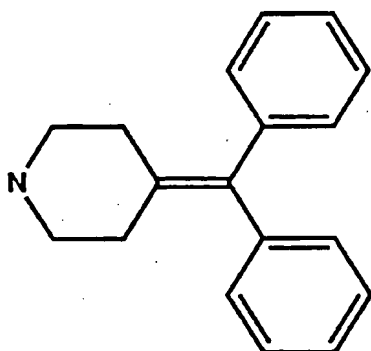
1. A piperidine derivative of general formula (I) or a pharmaceutically acceptable salt thereof:

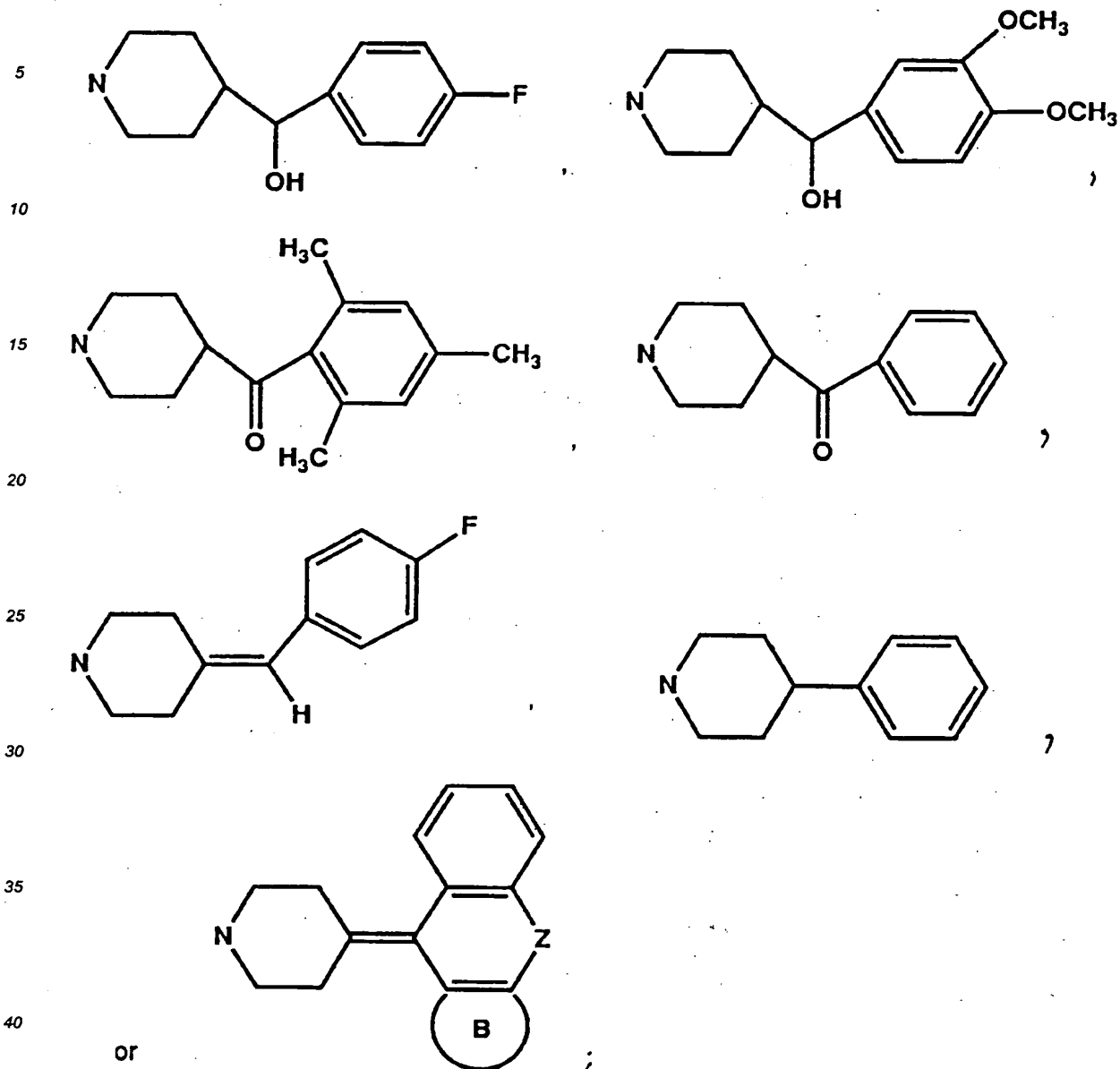


wherein

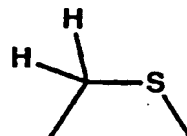
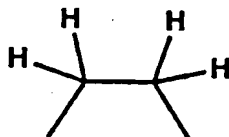
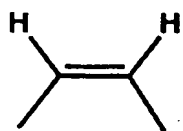


is any of the following groups:

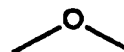
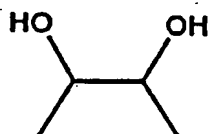
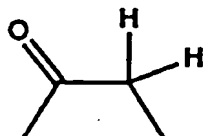




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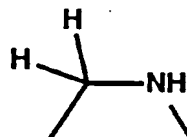
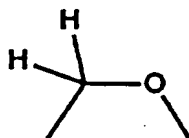
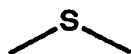


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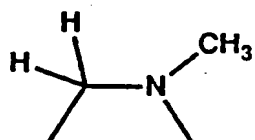
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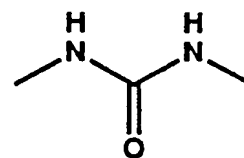
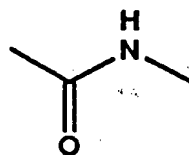
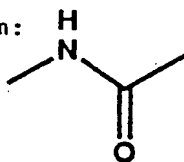
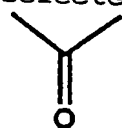
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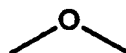
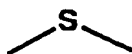
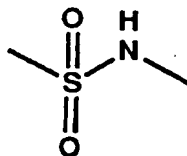


X is selected from:

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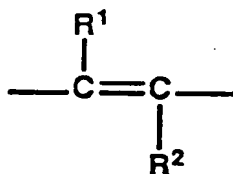
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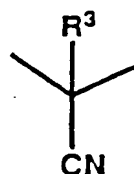
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or



wherein R¹ and R² are the same or different and are independently selected from hydrogen, methyl, ethyl, or propyl; R³ is hydrogen, alkyl of from 1 to 12 carbon atoms, or aryl of from 6 to 12 carbon atoms; Q is phenyl, cyclohexyl, piperidinyl, tetrahydropyranyl, pyridyl, pyrrolyl, N-methylpyrrolyl, thienyl, furyl, 1-hexyl, or cyano;

from 1 to 3 hydrogen atoms in Q may be independently substituted by alkyl of from 1 to 3 carbon atoms, perfluoroalkyl of from 1 to 3 carbon atoms, acylamino of from 1 to 6 carbon atoms, perfluoroacylamino of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, alkanesulfonylamino of from 1 to 3 carbon atoms, perfluoroalkanesulfonylamino of from 1 to 3 carbon atoms, acetoxo of from 1 to 3 carbon atoms, aminocarbonyl, aminosulfonyl, fluoro, chloro, cyano, hydroxy, nitro, amino, imidazolylmethyl, cinnamoylamino, p-fluorobenzoyl, cyanomethyl, cyanoethyl, methoxyacetoxo, alkoxycarbonyl of from 1 to 3 carbon atoms:

1 is an integer of from 0 to 1;

m is an integer of from 0 to 1;

n is an integer of from 0 to 6.

2. A piperidine derivative or pharmaceutically acceptable salt thereof according to claim 1 for use in the treatment of cardiac arrhythmia.
3. A piperidine derivative according to claim 1 which is any one of compounds 1 to 115 identified herein, or a pharmaceutically acceptable salt thereof.
4. A composition for treating cardiac arrhythmia comprising a mixture of a piperidine derivative or pharmaceutically acceptable salt thereof according to claim 1 and a pharmaceutically acceptable vehicle, diluent, carrier, extender, binder, swelling agent, lubricating or wetting agent, antiseptic, stabilizer, buffer, antioxidant, sweetener or flavour.
5. A composition according to claim 4 in unit dosage form.
6. A composition according to claim 5, containing from 0.2 to 500 mg of the piperidine derivative or pharmaceutically acceptable salt thereof.
7. A composition according to any one of claims 4 to 6 in the form of a tablet, capsule, elixir, or a sterile solution or suspension.
8. Use of a piperidine derivative or a pharmaceutically acceptable salt thereof according to claim 1 in the treatment of cardiac arrhythmia.
9. Use of a piperidine derivative or a pharmaceutically acceptable salt thereof according to claim 1 in the preparation of an antiarrhythmic agent.
10. A method of reducing or eliminating cardiac arrhythmia, comprising administering orally or parenterally an effective amount of a piperidine derivative or pharmaceutically acceptable salt thereof according to claim 1.
11. A method according to claim 10, in which the administration is an oral administration of a daily dose of from 0.001 to 2000 mg of the piperidine derivative or pharmaceutically acceptable salt thereof.
12. A method according to claim 10, in which the administration is a parenteral administration of a daily dose of from 0.001 to 1000 mg of the piperidine derivative or pharmaceutically acceptable salt thereof.
13. A method according to claim 10, in which the administration is of a unit dose of from 0.001 to 500 mg of the piperidine derivative or pharmaceutically acceptable salt thereof.